Exposure Assessment, Conceptual Modeling, Biomonitoring and Environmental Regulations

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Occupational/Environmental Exposure Definition

• Exposure is defined as contact over time and space between a person and one or more biological, chemical or physical agents (US NRC, 1991a).

-an ecological receptor and one or more biological, chemical or physical agents.

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- An **Exposure** is defined as the event when a person comes into **contact** with a toxic material. Coming into contact with a toxic material is a highly dynamic process that varies from person to person (depending on **behavior, location, and life style**) and from one toxic substance to another.

- The goal of Exposure Science is to identify and characterize ‘**real world’ contacts** with and uptake in the body of toxic materials that can cause acute or chronic health effects.

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Where Does Expose Assessment Fit Into the Risk Assessment Paradigm?

• Step 1 Hazard Identification (Toxicology and Epidemiology)
• Step 2, Dose-Response Assessment (Generally Toxicology and Environmental Epidemiology)
• Step 3, Exposure Assessment (Exposure Assessment Scientists- Assessors)
• Step 4, Risk Characterization (Risk Assessors)
• Step 5, Risk Communication

Guidelines for Exposure Assessment
Published on May 29, 1992, Federal Register 57(104):22888-22938
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Factors Influencing Human Exposure

- The duration, frequency and intensity of contact with the contaminant.  
  How Long/Often and Much?
- Identification of individual activity patterns, population distributions and susceptible populations.
**Exposure**

\[ E = \int_{t_1}^{t_2} C(t) \, dt \]

E is the magnitude of exposure, C(t) is the exposure concentration as a function of time, and \( t \) is time, \( t_2 - t_1 \) being the exposure duration (ED).

| Exposure | Contact of chemical with outer boundary of a person | concentration \( \times \) time | **Dermal** -- (mg chem/L water) \( \times \) (hrs of contact) (mg chem/kg soil) \( \times \) (hrs of contact)  
Respiratory -- (ppm chem in air) \( \times \) (hrs of contact) or (µg/m³ air) \( \times \) (days of contact)  
Oral -- (mg chem/L water) \( \times \) (min of contact) (mg chem/kg food) \( \times \) (min of contact) |
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Differences Between Exposure and Dose

- The term exposure refers to the concentration of an agent at the boundary between an individual and the environment as well as the duration of contact between the two, but dose refers to the amount actually deposited or absorbed in the body over a given time period (Hatch and Thomas, Measurement Issues in Environmental Epidemiology).
Internal (Absorbed ) Dose

The amount of a chemical penetrating across an absorption barrier or exchange boundary via either physical or biological processes.

Dose rate is mass of the chemical/time; the dose rate is sometimes normalized to body weight: mass of chemical/unit body weight • time

<table>
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<tr>
<th>Internal (Absorbed) Dose</th>
<th>Internal dose</th>
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<td><a href="http://www.pitt.edu/~cdv5/">http://www.pitt.edu/~cdv5/</a></td>
<td>[ D_{\text{internal}} = D_{\text{applied}} \int_{t_1}^{t_2} f(t) , dt ]</td>
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E, magnitude of exposure; \( t_2 \), exposure duration; \( w \), availability factor; \( C(t) \), exposure concentration as a function of time; \( IR \), ingestion or inhalation rate; \( f(t) \), nonlinear absorption function (Sexton et al., 1995a)

Dermal—mg chemical absorbed through skin
Respiratory—mg chemical absorbed via lung
Oral—mg chemical absorbed via g.i. tract

(dose rate: mg chemical absorbed/day or mg/kg • day)
Primary Routes of Human Environmental Exposure

- Dust, mist, fume, gas and/or vapor inhalation.
- **Dermal contact** with contaminated soils or dusts or contaminated water.
- **Ingestion** of contaminated food, water dusts and/or soil.

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Definition of Environmental Media -

• Air
• Surface Water
• Groundwater
• Sediment
• Soil
• Subsurface area
• Food Chain

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Important Terms

• Agent(s) - biological, chemical, physical, single agent, multiple agents, mixtures
• Source(s) - anthropogenic/non-anthropogenic, area/point, stationary/mobile, indoor/outdoor
• Transport/carrier medium - air, water, soil, dust, food, product/item
• Exposure pathways(s) - eating contaminated food, breathing contaminated workplace or ambient air, touching residential/municipal surfaces or bathing in contaminated water.

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Important Terms Continued

- **Exposure concentration** - mg/kg (food), mg/litre (water), μg/m³ (air), μg/cm² contaminated surface), fibres/m³ (air), percent by weight or ppm (mg/kg) for contaminated soils.
- **Exposure route(s)** - inhalation, dermal contact, ingestion, multiple routes.
- **Exposure duration** - seconds, minutes, hours, days, weeks, months, years, lifetime, population-generational.
- **Exposure frequency** - continuous, intermittent, cyclic, random, rare.
- **Exposure setting(s)** - occupational/non-occupational (environmental), residential/non-residential, indoors/outdoors, recreational/non-recreational.
- **Exposed population** - general population, population subgroups, individuals.
- **Geographic scope** - site/source specific, local, regional, national, international, global.
- **Time frame** - past, present, future, trends.

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What is a Conceptual Site Model?

• A written and/or pictorial representation of an environmental system and the biological, physical and chemical processes that determine the transport and fate of contaminants through environmental media to environmental receptors.

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Contraceptives, Female Hormone Replacement Drugs Household products- (Detergents Shampoo etc.)

Soil and Vadose Zone
  - Runoff
  - Leaching
  - Deposition
  - Direct Contact
  - Ingestion

Surface Water
  - Sedimentation
  - Resuspension
  - Direct Contact
  - Ingestion, Food Chain

Groundwater
  - Direct Contact
  - Ingestion

Aquatic Ecological Receptors
  - N/A
  - Gills, Dermal, Ingestion
  - Ingestion, Food Chain
  - NA

Terrestrial Ecological Receptor
  - Dermal, Ingestion
  - Dermal, Ingestion
  - NA

Humans
  - Dermal, Ingestion
  - Dermal, Ingestion
  - Dermal, Ingestion

WWTP
Modeling – Mercury in New Jersey Wells
“Biomonitoring” and “Biomarkers” - Definitions

- “Biomonitoring” is the analytical measurement of biomarkers in specified units of tissues or body products (blood, urine, etc.) (Environmental Health Perspectives-November, 2006).

- “Biomarkers” are any substances, structures, or processes so measured that indicate an exposure or susceptibility or that predict the incidence or outcome of disease (Toniolo et al. 1997).
Exposure and Biomarkers of Exposure, Leading to Disease

Figure 1. A schematic representation of markers of exposure, response, and susceptibility in the exposure–disease continuum: an example for PAHs and cancer. CYP2A6, cytochrome P4502A6 gene; ETS, environmental tobacco smoke; GSTM1, glutathione S-transferase M1 gene; PAHs, polycyclic aromatic hydrocarbons; Arrows indicate predictability of each marker for exposure or disease in the exposure–disease continuum. Adapted from NRC (1987). PAHs in ETS and urban air are a marker for exposure source. GSTM1 null genotype and blood PAH–DNA adducts are independent markers of cancer case status (disease) but have a multiplicative effect in combination (Perera et al. 2002; Tang et al. 1995). GSTM1 null genotype is a predictor of tissue PAH–DNA adducts, which are a marker for altered function (Perera et al. 2002; Rundle et al. 2000; Tang et al. 1995). CYP2A6 variant is a marker for increased internal dose of nicotine and protective effect on cancer development (Spitz et al. 2005). Plasma cotinine is a marker for internal exposure to ETS but is not correlated with blood PAH–DNA adducts (Mooney et al. 2005). Blood PAH adducts are a marker for PAH/ETS exposure, internal dose, biologically effective dose, early biologic response, and cancer (Mooney et al. 2005; Perera et al. 2002, 2004; Poirier and Beland 1992; Veglia et al. 2003; Whyatt et al. 1998). Tissue PAH–DNA adducts are a marker for altered function and cancer (Rundle et al. 2000).

Personalized Exposure Assessment: Promising Approaches for Human Environmental Health Research Environmental Health Perspectives • VOLUME 113 | NUMBER 7 | July 2005.
What is a Biological Marker of Exposure?

A biological marker of exposure is defined as a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (US NRC, 1989; IPCS, 1993)-after exposure to the xenobiotic contaminant or a physical exposure, such as ionizing radiation.
Biomonitoring-General

- Biological markers represent a means to monitor environmental exposure by characterizing an individual's total dose of a contaminant from all sources of exposure. Remember that dose is mass of contaminant over some time.

- The main advantage of this strategy is in evaluation of an individual's total exposure using a measure which integrates over all exposure sources and is influenced by human behavior.

- Biological markers are believed to be more predictive of health effects than external measures of exposure.

- Biological markers address important exposure assessment needs:
  - characterizing an individual's or a population's exposure
  - generating population distributions of dose
  - identifying the environmental and demographic determinants of exposure.
Disadvantages of Biological Monitoring

• The main disadvantage of biological markers is the difficulty in characterizing the individual sources which contribute to the subject's total exposure.

• When developing and utilizing biological markers, understanding the toxicokinetics of the contaminant in the system is crucial to characterize the biological variability and to determine whether the biological marker is valid for exposure assessment purposes at the concentration of interest.

• There is an ethical concern in relying on biomonitoring – especially in known occupational exposure assessment.
Situations which are best suited for biological monitoring.

Ideally, a biological marker of exposure should be:

1. Chemical-specific.
2. Detectable in trace quantities.
3. Available by non-invasive techniques.
4. Inexpensive to assay.
5. Relate consistently and quantitatively to the extent of exposure and ideally also integrate the exposure over time (Bond et al., 1992).

Currently there are very few biological markers that possess all these characteristics.
Sampling of Blood

- Blood is frequently used for biological monitoring, especially in clinical settings such as occupational medicine.

- Blood can integrate all sources of exposure, including internal sources, and provide an indication of current internal dose.

- Since blood transports all agents throughout the organism, it represents an opportunity to sample all types of contaminants, such as gases, solvents, metals and fat-soluble compounds.
Sampling of Urine

- The concentrations of compounds found in urine usually reflect time-weighted averages in plasma during collection and storage in the bladder (Que Hee, 1993).
- The presence of a contaminant or its metabolite in urine generally represents recent exposure, though in some cases it may represent release from storage within the body (Lauwerys, 1983). (Release of lipopolyic chemicals from adipose tissue during weight reduction is an example of release from body storage.)
- Urine can be analyzed for metabolites of organic chemicals (e.g., benzene and styrene), metals (e.g., arsenic and mercury) and pesticides as well as for mutagenic potential (Lauwerys, 1983; Baselt, 1988; Que Hee, 1993).
- Since collection of urine samples is non-invasive, some investigators feel that, when validated, urine may be a better sampling medium than blood for monitoring (Smith & Suk, 1994).
Exhaled Breath

• Breath analysis is useful for assessing recent exposure to gases (e.g., carbon monoxide) and organic vapors and solvents (e.g., acetone and toluene).
Saliva Sampling

Glands at four locations in the mouth produce saliva; the secretion rate varies at each location. Chemicals enter saliva via passive diffusion from plasma. Therefore, saliva may become a useful tool to non-invasively characterize plasma levels of contaminants (Silbergeld, 1993).

Social science research has used saliva sampling because of its ease of collection and storage (Dabbs, 1991, 1993). Contaminants found in saliva include cotinine, drugs, metals, organic solvents, pesticides and steroid hormones (Tomita & Nishimura, 1982; Nigg & Wade, 1992; Silbergeld, 1993).
Sampling Keratinized Tissues (hair and nails)

- Keratinized tissues, primarily hair and toenails, are practical sampling media for evaluation of past exposure to metals (Bencko et al., 1986; Bencko, 1991; Subramanian, 1991; Kemper, 1993, Bencko, 1995).
- Toenails are usually the medium of choice because these media:
  - integrate exposures over a period of months.
  - contain relatively larger concentrations of trace elements than blood or urine and
  - are easy to collect, store and transport (Garland et al., 1993; Kemper, 1993).
Bone Sampling

- Bone represents both past exposure to bone-seeking elements and is a source for future internal exposure to these elements. The concentrations of elements in bone represent long-term exposure and storage of contaminants. For example, the half-life of lead in bone is approximately 10-40 years (Rabinowitz, 1991).

- Although numerous elements can be detected in bone tissue using destructive analyses such as atomic absorption spectroscopy (AAS), \textit{in vivo} measurement of environmental contaminants in bone has been limited to lead (e.g., Somervaille et al., 1988; Hoppin et al., 1995).

- Lead concentration in bone can be analyzed non-invasively using a technique known as X-ray fluorescence (XRF) (Hu et al., 1995).

- Epidemiological studies have established that bone-seeking a-particle-emitting radionuclides are effective sarcomagenic agents, increasing tumor incidence by up to 1000-fold in exposed individuals (H. S. Martland and R. E. Humphries, Osteogenic sarcoma in dial painters using luminous paint. \textit{Arch. Pathol.} \textbf{7}, 406 (1929) and C. Mays and H. Spiess, Bone sarcomas in patients given 224Ra. In \textit{Radiation Carcinogenesis: Epidemiology and Biological Significance} (J. B. Fraumeni, Ed.), pp 241–252. Raven Press, New York, 1982.)
Breast Milk Sampling

• Breast milk sampling represents a non-invasive method to estimate body burden of contaminants in adipose tissue. The correlation between contaminant concentrations in the lipid phase of milk and adipose tissue is good (Sim & McNeil, 1992).

• Environmental studies have used breast milk to evaluate past exposure to lipophilic chemicals (e.g., pesticides and PCBs) and metals (WHO, 1996b) and to examine potential exposures for breast-feeding infants (Niessen et al., 1984; Davies & Mes, 1987; Sikorski et al., 1990; Sim & McNeil, 1992).

• Organic chemicals found in breast milk have high lipid solubility, resistance to physical degradation or biological metabolism and slow or absent excretion rates (Rogan et al., 1980). Breast milk represents a major route of excretion of lipophilic chemicals for lactating women (Rogan et al., 1980; Sim & McNeil, 1992).

• Concentrations of chemicals in breast milk are a function of parity, age, body mass, time of sampling, nutritional status, lactation period and fat content of milk (Rogan et al., 1986; Sim & McNeil, 1992). Breast milk results are generally standardized to milk fat levels.
Sampling Adipose Tissue

- Exposure assessment studies using adipose tissue have been limited primarily to ecological studies comparing fat from cadavers or surgical specimens to general pollution levels.

- Adipose tissue represents a long-term reservoir of lipophilic compounds that the body slowly metabolizes and may release into the bloodstream.

- Unfortunately there is no non-invasive manner to sample fat stores directly, and many subjects see fat sampling as exceedingly invasive.

- WHO Human Exposure Assessment
Sampling Feces

• Most often used for bacteriological exposure sampling.
• Feces are a highly fat-soluble medium that provides information on compounds of high-molecular weight that exit the body via biliary excretion (metabolism by liver and excretion via bile) and on unabsorbed chemicals that enter the body via ingestion.

Main Text for Biomonitoring Material Extraction-WHO Exposure Assessment
Examples of National Biomonitoring Programs

• National Health and Nutrition Examination Survey (NHANES)- Centers for Disease Control and Prevention
• CDC National Environmental Public Health Tracking Program, UPACE –Center of Excellence
• Interagency National Children’s Study
• Farm Family Exposure Study (University of Minnesota)
The Basis for Biomonitoring
Ecological Receptors as Sentinels for Human Exposure

• Contaminants in sediments and water bioaccumulate in aquatic food chains and concentration levels can be magnified over 100X in higher trophic level feeders.
• Lipophilic (hydrophobic) chemicals are more rapidly exchanged between the water and organism than they are excreted or biodegraded by the organism.
• Methylmercury is bioaccumulated in the muscle-fillet tissue of fish-particularly pisciverous fish.
• Fish classically bioaccumulate lipophilic steroid estrogens and estrogen mimicking chemicals such as estrone (E1), 17-ethinylestradiol (EE2), NP-nonylphenol, DDT and PCB’s. These are also stored in human adipose tissue.
Reasons for Biomonitoring Non-Human Species-Continued

• Establish the exposure and thus risk to humans from consumption of contaminated foods-especially fish (incredibly important to tribal groups and vulnerable sub-populations- Amish, immigrant Asians, African Americans).

• To establish the efficacy of and use aquatic and other species as sentinels for human health effects.

• To determine population risk from contaminant exposure to a species or an ecosystem.
Channel Catfish, Hg in fillet, 95% CI
Occupational and Environmental Health Legislation

• Occupational Safety and Health Act of 1970-
  Adopted the 1968 American Conference of
  Governmental Industrial Hygienists (ACGIG),
  Threshold Limit Values (TLV’s) for airborne
  contaminants.

- A TLV is an exposure concentration that most
  workers can be exposed to 8 hours/day, 40
  hours/week over a working lifetime with no
  adverse effect.
Occupational and Environmental Health Legislation

• Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA)- commonly called Superfund
  -To provide for remediation of sites not cleaned-up by the responsible party.
  -To establish priorities for the clean-up of the nation’s worst toxic and radiological waste sites.
CERCLA continued.

- Conduct human and ecological risk assessments through the Agency for Toxic Substances and Disease Registry (ATSDR).
- Conduct remedial investigation and feasibility studies.
Occupational and Environmental Health Legislation

• Resource Conservation and Recovery Act of 1976 (RCRA)
  - Creates cradle to grave regulatory scheme to manage, store, transport and dispose of hazardous waste.
  - Designed to prevent current hazardous waste disposal from causing future environmental health problems.
Clean Air Act of 1970

• A comprehensive Federal law that regulates air emissions from area, stationary, and mobile sources.

• Authorizes the EPA to establish National Ambient Air Quality Standards (NAAQS) to protect public health and the environment.
Clean Water Act

• Started out as the Federal Water Pollution Control Act Amendments of 1972 and has been amended many times.

• This act set up the structure for regulating discharges of pollutants into U.S. waters.

• Includes construction of sewage plants, water quality criteria for surface waters, and pollution control programs for industrial plants.
Safe Drinking Water Act of 1974

- Established a national structure for drinking water protection activities.
- Authorized EPA to establish national, enforceable health standards for contaminants in drinking water.
Toxic Substances Control Act (TSCA) of 1976

- EPA tracks the 75,000 industrial chemicals currently produced or imported into the U.S.
- EPA repeatedly screens these chemicals and can require reporting or testing of those that may pose an environmental or human-health hazard.
- EPA can ban the manufacture and import of those chemicals that pose an unreasonable risk.